Human Leukocyte Antigen Concordance and the Transmission Risk via Breast-Feeding of Human T Cell Lymphotropic Virus Type I

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Objective. We examined the association between mother-to-child human T cell lymphotropic virus type I (HTLV-I) transmission and human leukocyte antigen (HLA) class I types.

Methods. In 1989, children born to HTLV-I–infected mothers in Jamaica were enrolled and prospectively evaluated for HTLV-I infection. HLA class I types in mothers and children were determined by DNA-based polymerase chain reaction methods. Associations between HLA class I types and transmission of HTLV-I were analyzed using proportional-hazards regression models adjusted for the duration of breast-feeding. Transmission risk in children still breast-feeding at 12 months was determined using actuarial methods.

Results. Of 162 children, 28 (17%) became infected. After Bonferroni's adjustment for multiple comparisons, the transmission risk was not influenced by any specific HLA class type or the A2 supertype. However, compared with children who shared 3 HLA class I types with their mothers (the minimum number possible), the transmission risk increased 1.8-fold with 4 shared types and 3.0-fold with 5 or 6 shared types ($P_{trend} = .039$; 1.75-fold increase for each additional concordant HLA type). This association was independent of maternal HTLV-I proviral level, antibody titer, and household income.

Conclusions. We found a significant dose-response relationship between HTLV-I transmission via breast-feeding and mother-child HLA class I type concordance. Immunological interactions between a child's cells and maternal cells may influence the risk of HTLV-I infection by breast-feeding, perhaps because antigens on maternal cells are seen by the child as being "self."

Retroviruses can be transmitted from mother to child. For human T lymphotropic virus type I (HTLV-I), the predominant route of transmission to children is via infected breast milk [1, 2]. Only ~3%–4% of children become infected if they are not breast-fed or are breast-fed for <6 months [3], and the transmission risk increases with the duration of breast-feeding. The cumulative risk of infection in children who are regularly breast-fed is ~20% [2, 4]. Furthermore, the transmission risk increases with the amount of provirus in breast milk [5]. Breast milk proviral levels also correlate with proviral levels in maternal peripheral blood mononuclear cells (PBMCs) and with antibody titers [5]. It is therefore not surprising that the transmission risk correlates with proviral and antibody levels in maternal peripheral blood [4, 6]. However, these associations do not explain why the majority of children who are breast-fed for long periods do not become infected.

Although it is more commonly transmitted in utero or perinatally, HIV can also be transmitted by breast-feeding [7, 8]. As with HTLV-I, transmission occurs in proportion to the duration of breast-feeding [7, 8], and the risk increases when mothers have high HIV provirus levels in breast milk, which are also directly correlated with peripheral blood provirus levels [9]. The sentinel

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observation that inspired the present study was that mother-to-child in utero and perinatal HIV transmission was more likely when children were more concordant with their mothers in HLA class I type [10, 11]. In one study, children with HLA class I type A*02 [10] (later reported to be the A2 supertype [12]) had a decreased risk of early infection. With HIV, transmission via breast-feeding was not reported to be associated with HLA class I type variability [10, 11], whereas, with HTLV-I, vertical transmission almost always occurs via breast-feeding. However, unlike HIV, HTLV-I is transmitted primarily by cell-to-cell contact rather than by free virus [13, 14]. We reasoned that factors affecting cellular immunity might be more important for the vertical transmission of HTLV-I than for HIV. Because HLA is an important component of cellular immunity, we therefore studied whether specific HLA class I types or concordance between mother and child were associated with the risk of mother-to-child HTLV-I transmission.

SUBJECTS, MATERIALS, AND METHODS

HTLV-I is endemic in Kingston, Jamaica, our study site. In 1989–1990, we enrolled women attending antenatal clinics and who provided informed consent into a prospective study of mother-to-child HTLV-I transmission. Of 212 HTLV-I–infected mothers and their children who enrolled, 162 completed at least 18 months of follow-up and are the basis of the present analysis. To date (and to the best of our knowledge), this is the largest cohort of children born to HTLV-I–infected women who have been prospectively monitored for mother-to-child HTLV-I infection and have provided samples to assess maternal viral and antibody levels. Details and results of the study have been published elsewhere [2, 4, 5, 15]. The benefits of breast-feeding in reducing morbidity and mortality, especially that due to gastrointestinal diseases, are well established and outweigh the risks of HTLV-I infection [16]. However, in recent years, mothers known to be infected with HTLV-I have been encouraged to limit the duration of breast-feeding to <6 months, if possible. The present study was approved by ethical review boards at the University of the West Indies, Kingston, Jamaica, and at the National Cancer Institute, Bethesda, Maryland.

At enrollment, demographic and pregnancy information was recorded, and blood samples were obtained from mothers. After birth, children born to these mothers returned at ages 6 and 12 weeks, quarterly up to age 24 months, and semiannually thereafter. At each visit, an interval medial history was obtained, physical examination was performed, and blood samples were obtained. The duration of breast-feeding was calculated from the date of birth to the midpoint between the date of the clinic visit at which the mother reported having stopped breast-feeding and the preceding clinic visit. HTLV-I antibody was detected serologically using a whole-virus EIA (DuPont) with confirmation by Western blotting (Cambridge-Bioscience). Titers were assessed by reactivity (Vironstika HTLV-I/II Microelisa System; Organon-Teknika) in samples diluted 5-fold and are reported as the reciprocals of the end-point positive dilutions. Infections in seroconverting children were verified by polymerase chain reaction (PCR) for HTLV-I *tax* sequences in serial PBMCs, using methods described elsewhere [2, 4, 5]. Provirus sequences were sought in triplicate extracts of ~50,000 cells, each run on an ABI PRISM 7700 sequence detector (Applied Biosystems). Infections were assumed to have occurred at the midpoint between the last negative and the first positive indication of infection; in most instances, this positive indication was based on PCR results, but, in a few older children who did not provide cell samples, it was based on the new detection of HTLV-I antibody. For the assessment of maternal HTLV-I proviral levels, measured as the $\log_{10}$-transformed copy number per 10^6 cells, we used real-time PCR methods, described elsewhere [4, 5], to target the same *tax* sequences as those used for the PCR analysis of children's samples.

For HLA class I type analysis, DNA was extracted from PBMCs from mothers and children. We tested for HLA-A, -B, and -C class I alleles by the sequence-specific oligonucleotide probe method. Alleles were grouped by their serologic antigenic equivalents, called types, in parallel with the approaches used in analyzing HLA class I alleles in HIV studies [10, 11]. Direct sequencing of the allele was done when necessary and on all A*02 samples to determine whether they were of the A2 supertype (*0201, *0205, *0214, *6801, *6802, and *6901) [12]. At least 1 HLA-A, -B, and -C class I type was identified for each subject, and persons with only 1 type identified were considered to be homozygous for that type. With this approach, we had no unidentified HLA types. We did not examine HLA class II alleles, because of their great heterogeneity. For HLA class II type analyses, an appropriately powered study would have required a larger data set than what we had available. However, in one study, HLA class II types were not associated with HIV mother-to-child transmission [11].

We initially examined whether specific HLA class I types affected the transmission risk. Because the effect might have been a factor in either mother or child, we examined each group separately. Each specific HLA class I type present in at least 16 (10%) of the 162 mothers or children in the study was analyzed as a dichotomous variable. HLA class I type concordance between mother and child was assessed by how closely the mother's HLA class I type matched the child's HLA class I type. Each child inherited 1 HLA class I type at the HLA-A, -B, and -C loci from the mother, resulting in a minimum of 3 matched types (1 for each HLA class I type). When the mother was homozygous for a given type, the child necessarily matched this type on both maternal chromosomes, resulting in a score of 2 for that maternal HLA class I type. Some children also inherited types from the father that, by chance, matched those of the mother. Therefore, each child matched the maternal HLA types at 3 (only HLA types inherited from a heterozygous mother) to 6 HLA types (all HLA types matched those found on the 2 maternal chromosomes). This convention was used in previous reports of the relationship between HLA class I type and HIV [10, 11]. For robustness, we also grouped concordance levels 5 and 6 ("5/6") in the analysis.

In the present study, all children were breast-fed, and the transmission risk increased directly with the duration of breast-feeding [2, 4]. Follow-up was stopped at the end of breast-feeding, at the time of the last HTLV-I test if children were still breast-feeding (3 children), or at the time of infection, whichever came first. Seven children had estimated ages at infection that occurred after the end of breast-feeding (median duration, 3.8 months) because they were HTLV-I negative at the end of breast-feeding but HTLV-I positive at the time when the next sample was obtained. We attribute these infections detected after breast-feeding ended infections occurring near the end of breast-feeding and recorded the time of infection as occurring at the end of breast-feeding.

Hazard ratios (HRs) with 95% confidence intervals (CIs) were examined using Cox proportional-hazards regression analysis (PROC PHREG version 8; SAS Institute), with the time of infection treated as a discrete variable. Concordance was treated as a dummy variable, and mother-child pairs with 3 matched HLA class I types served as the reference category. Trends across categories were analyzed by treating concordance level as a categorical variable (P for trend [P_{trend}]). We examined the possible confounding or effect modification by known maternal risk factors affecting the transmission risk using models that included maternal HTLV-I proviral levels, antibody titer, and income. Variables were categorized using criteria published elsewhere [4]. Maternal antibody and proviral levels were closely correlated [4] and were therefore analyzed in separate models as log-transformed continuous variables. Household income at enrollment was examined because it had previously been found to be an independent risk factor for transmission [2, 4]. Four mothers had twins, and 2 mothers delivered twice during the study period. Each child was analyzed as a separate birth. To avoid confounding due to a common mother for multiple children, we also reanalyzed the final model after excluding each of the second-born twins and the older child in the sibling pairs. Analysis of individual HLA class I types was limited to those present in >10% of mothers or children (i.e., at least 16 persons). To avoid chance findings due to multiple comparisons, we adopted the Bonferroni adjustment to determine significance. P values are 2-sided, unless otherwise indicated. We also examined the transmission risk by concordance strata using Kaplan-Meier actuarial methods.

RESULTS

Of 162 children born to HTLV-I–infected mothers, most were black (1 was East Indian; 5 were of unspecified race). The mean duration of breast-feeding was 12.6 months (range, 0.4–44.0 months). Mastitis was described in 4 instances and was not temporally related to HTLV-I transmission. Supplemental feeding with solid foods was usually started between 3 and 4 months of age.

During the study, 28 (17%) children became infected, and the average age at infection was 14.1 months. No single HLA class I type in mother or child was significantly associated with transmission risk after correction for multiple comparisons. Similarly, there was no association between transmission risk and homozygosity at any specific type in either mother or child. The A2 supertype was found in 85 mothers (who had 15 infected children) and in 76 children (12 of whom became infected). Transmission risk was not associated with the A2 supertype (HR, 1.1 [95% CI, 0.5–2.4] and HR, 0.9 [95% CI, 0.4–1.8], respectively, in mothers and children).

The distribution of HLA class I type concordance between mothers and children is presented in table 1. After adjustment for breast-feeding duration, HR of infection increased from 1.0 (reference) with 3 matched types to 1.8, 2.8, and 4.1 with 4, 5, and 6 matched HLA class I types, respectively ($P_{\text{trend}} = .037$). Because only 4 children were concordant with their mother for 6 HLA class I types, we thereafter combined data from children with 5 and 6 concordant types. Compared with those having 3 matched types, the HR for children with 5/6 matched types was 3.0 (95% CI, 1.0–9.5), and the risk increased with increasing concordance ($P_{\text{trend}} = .039$) (table 2). The transmission risk increased an average of 1.75-fold with each increase in the level of concordance (3, 4, and 5/6).

The HLA class I type concordance level was not significantly associated with the maternal proviral level, antibody titer, or income. Adjusting the models by these variables slightly increased the association between HLA class I type concordance and transmission risk, but the changes were not statistically significant (table 2). In an analysis that limited the data set to 1 child per mother ($n = 156$, with 28 infections), the HRs for HLA class I type concordance and HTLV-I transmission risk were essentially unchanged.

On the basis of these findings, we postulated that children who had greater HLA class I type concordance with their mothers would become infected at younger ages. The trend toward an increasing transmission risk with greater concordance was significant when the Cox test was used for life-table data (1-sided $P = .04$; figure 1). Among children who were still breast-feeding at 12.0 months, 14% of those with 3 matched HLA class I types with their mothers were infected, compared with

Table 1. Individual hazard ratios (HRs) and 95% confidence intervals (CIs) for variables considered in models of mother-to-child transmission risk for 162 children born to human T cell lymphotropic virus type I (HTLV-I)–infected mothers.

Model, stratum	Total, no.	HTLV-I infected, no.	HR (95% CI)[a]
HLA class I type concordance			
3	93	12	1.0 (Reference)
4	53	12	1.8 (0.8– 4.0)
5	12	3	2.8 (0.8– 9.9)
6	4	1	4.1 (0.5–32.6)
Mother's weekly income, Jamaican $			
>200	69	6	1.0 (Reference)
101–200	57	12	2.2 (0.8– 5.9)
⩽100	34	10	3.4 (1.2– 9.5)
Unknown	2	0	
Mother's HTLV-I antibody titer (reciprocal)			
<1000	37	1	
1000–4000	38	3	
4001–10,000	38	10	3.1 (1.7–5.6)[b]
>10,000	42	14	
Unknown	7	0	
Mother's HTLV-I proviral level, $\log_{10}$ copy no./10^6 cells			
<2.20	58	2	
2.20–3.10	50	10	2.6 (1.6–4.3)[b]
⩾3.11	35	13	
Unknown	19	5	

[a] Adjusted for duration of breast-feeding only.
[b] Per $\log_{10}$ increase.

16% of those with 4 matched HLA class I types and 38% of those with 5/6 matched HLA class I types.

DISCUSSION

In the present study, the transmission risk for HTLV-I increased 1.75-fold with each increase in concordance from 3 to 4 to 5/6 matched HLA class I types. As had been expected, we observed previously reported risk factors for the transmission of HTLV-I via breast-feeding in Jamaica [4], including maternal proviral levels and antibodies, as well as income. In bivariate models, the relationship between HLA class I type concordance and HTLV-I transmission risk was not altered by including these important risk factors, which indicates that HLA class I type concordance had an independent effect on transmission risk.

Mother-to-child HTLV-I transmission is frequent in breast-fed children [1, 2] but is uncommon in those who are completely bottle-fed [3]. Therefore, the child's primary exposure to HTLV-I must be via breast milk, and the site of infection must be in the alimentary tract. At the cellular level, HTLV-I infection occurs by cell-to-cell interaction, not by free virus [13, 14]. We hypothesize that maternal lymphocytes survive destruction by the child's gastric digestion, perhaps because of rapid transit through the stomach and because breast milk, being alkaline, neutralizes the effect of stomach acids. Intact maternal cells reaching the gastrointestinal mucosa then interact with the child's lymphocytes or dendritic cells in the luminal crypts. As part of the normal gastrointestinal immune system, the child's lymphocytes circulate between the luminal crypts and regional lymph nodes. If they become infected by contact with infected maternal cells in the gastrointestinal crypts, they can reenter circulation and thereby spread infection. Additionally, perhaps intact and viable maternal cells also enter the child via the gastrointestinal crypts and carry HTLV-I provirus with them. If these maternal cells are not recognized as foreign because they are HLA concordant, they might persist. Either way, cell-to-cell interactions between maternal and child cells occur.

Even in breast-fed children, the transmission of HTLV-I is uncommon within the first months of life [3], which suggests that NK-mediated antiviral innate immunity [17] is protective. However, over time, the protection decreases, so that most infected children acquire infection after age 6 months [2, 4]. The timing correlates with decreasing levels of maternal antibodies. We speculate that, during the early months of the first year of life, mother-to-child HTLV-I transmission is prevented by antibody-dependent cellular cytotoxicity (ADCC) acting in conjunction with innate immunity, with maternally acquired antibody being the source of HTLV-I–specific antibody in the child. Several in vitro studies have shown that ADCC is operative

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) of human T cell lymphotropic virus type I (HTLV-I) transmission risk by HLA class I type concordance level, both unadjusted and adjusted for maternal variables affecting the risk of mother-to-child transmission.

		Adjusted HR (95% CI)		
HLA class I type concordance	Unadjusted HR (95% CI)	Income, Jamaican $	Maternal HTLV-I antibody titer	Maternal HTLV-I proviral level, $\log_{10}$ copy no./10^6 cells
3	1.0 (Reference)	1.0	1.0	1.0
4	1.8 (0.8–4.0)	1.8 (0.8–4.0)	1.8 (0.8–4.0)	1.7 (0.7–4.0)
5/6	3.0 (1.0– 9.5)	2.9 (0.9–9.7)	3.3 (1.0–10.8)	3.5 (1.1–11.6)
P_{trend}	.039	.051	.031	.039

NOTE. All HRs were adjusted for the duration of breast-feeding.

against HTLV-I–infected cells [18–20], including one that showed that NK activity against HTLV-I–infected cells can be mediated by HTLV-I–specific antibody [21]. When maternally acquired HTLV-I–specific antibody levels decrease, ADCC no longer functions, and the child becomes vulnerable to HTLV-I infection. This hypothesis might be explored by studies in animal models. However, ADCC alone does not explain the role of HLA class I type concordance.

HTLV-I is passed between lymphocytes via synapses that have been reported to be virally induced and independent of cell-surface markers [13, 14]. Yet we have strong in vivo evidence that HLA class I type concordance is important to the transmission of HTLV-I between cells. There could be enhanced transmission because of greater cell-to-cell interaction occurring in the context of HLA class I type concordance. Alternatively, there may be a greater persistence of infected maternal cells when they are HLA class I type concordant with those of the child, because they are less efficiently recognized as foreign and therefore eliminated by the innate immune system. The presence of "self" HLA class I antigens on lymphocytes is known to activate NK-inhibitor receptors and to suppress the immune responses [22].

Our findings demonstrate that HLA class I type concordance increases the mother-to-child transmission risk for HTLV-I, as has been observed for HIV [10, 11]. The relationship between maternal-child HLA class I type concordance and transmission risk should be explored in other vertically transmitted viruses and with in vitro studies. It is also possible that this enhanced susceptibility due to immunological concordance operates in horizontally transmitted infections. Recent reports have suggested that HLA type matching, when it occurs, might increase the transmission risk of HIV between sex partners [23, 24]. However, close HLA class I type concordance between randomly assorted couples would be infrequent, compared with that in mother-child pairs, in whom there are at least 3 shared HLA class I types.

MacDonald et al. [10] noted a significantly lower risk of mother-to-child HIV transmission when children had an HLA A02 type or the A2 supertype [12]. Independently, HLA B18 (but not A02) type was reported to protect against both early and breast-feeding HIV-1 transmission [25]. In a more-complex model, specific HLA B alleles were proposed to interact with the NK recognition repertoire to increase or reduce the HIV transmission risk through adaptive and innate immune mechanisms [26]. In contrast, Polycarpou et al. [11] did not find associations with specific HLA types in their mother-to-child HIV-1 transmission study. Similarly, we did not observe associations between HTLV-I transmission via breast-feeding and the A*02 type, the A2 supertype, any B* type, or any other specific HLA type. However, because of limited numbers in our study, we could have missed weak but true associations or associations with uncommon alleles.

In summary, we found HLA class I type concordance to be an important factor affecting the transmission of HTLV-I via breast-feeding. How retroviruses are transmitted remains unclear. The present findings may provide insight into the im-

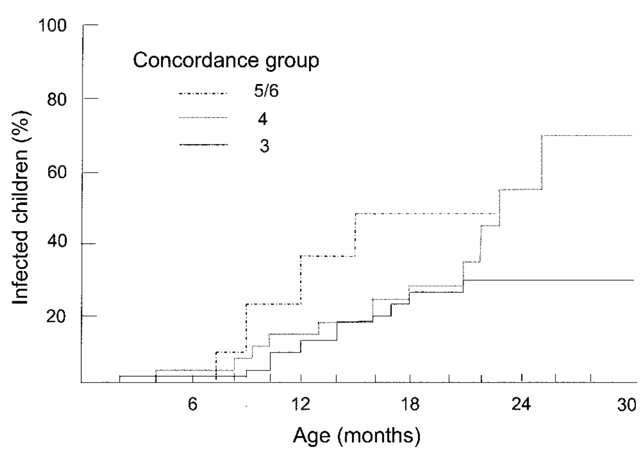

Figure 1. Human T cell lymphotropic virus type I (HTLV-I) transmission risk by age, stratified by HLA class I type concordance level, in 162 children born to HTLV-I–infected mothers.

munological mechanism of HTLV-I transmission and an inducement to further in vitro research.

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